Practitioner's Docket No. 2544/112

CHAPTER II

Preliminary Classification:

Proposed Class:

Subclass:

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US)

(ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/EP00/05735	21 June 2000 (21.06.00)	05 July 1999 (05.07.99)
International Application Number	**International Filing Date**	**International Earliest Priority Date**

TITLE OF INVENTION: Therapeutic Agents
APPLICANT(S): Knoll Aktiengesellschaft

Box PCT
Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

CERTIFICATION UNDER 37 C.F.R. SECTION 1.10*
*(Express Mail label number is **mandatory**.)*
(Express Mail certification is optional.)

I hereby certify that this paper, along with any document referred to, is being deposited with the United States Postal Service on this date, January 4, 2002, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number EL603031578US, addressed to the: Commissioner for Patents, Washington, D.C. 20231.

Harriet M. Strimpel, D. Phil.
(type or print name of person mailing paper)

Harriet Strimpel
Signature of person mailing paper

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1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. Section 371:

a. This express request to immediately begin national examination procedures (35 U.S.C. Section 371(f)).

b. The U.S. National Fee (35 U.S.C. Section 371(c)(1)) and other fees (37 C.F.R. Section 1.492) as indicated below:

2. Fees

CLAIMS FEE*	(1) FOR	(2) NUMBER FILED		(3) NUMBER EXTRA	(4) RATE	(5) CALC-ULATIONS
	TOTAL CLAIMS	40	-20 =	20	x $18.00 =	$360.00
	INDEPEN-DENT CLAIMS	23	- 3 =	0	x $84.00 =	$0.00
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $280.00					$280.00
BASIC FEE	The international search fee, as set forth in Section 1.445(a)(2) to be paid to the USPTO acting as an international Searching Authority: where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $890.00					$890.00
	Total of above Calculations					= $1,530.00
SMALL ENTITY	Reduction by 1/2 for filing by small entity, if applicable. Affidavit must be filed. (note 37 CFR Sections 1.9, 1.27, 1.28)					- $0.00
	Subtotal					$1,530.00
	Total National Fee					$1,530.00
	Fee for recording the enclosed assignment document $40.00 (37 C.F.R. Section 1.21(h)). See attached "ASSIGNMENT COVER SHEET".					$0.00
TOTAL	Total Fees enclosed					$1,530.00

*See attached Preliminary Amendment Reducing the Number of Claims.

A check in the amount of $1,640.00 to cover the above fees is enclosed.

3. A translation of the International application into the English language (35 U.S.C. Section 371(c)(2)) is not required as the application was filed in English.

4. Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. Section 371(c)(3)) are transmitted herewith.

5. A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. Section 371(c)(3)) has not been transmitted for reasons indicated in section 5.

6. A copy of the international examination report (PCT/IPEA/409) is attached..

7. An oath or declaration of the inventor (35 U.S.C. Section 371(c)(4)) complying with 35 U.S.C.

Section 115 will follow.

II. Other document(s) or information included:

8. An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a) is attached.

9. An Information Disclosure Statement under 37 C.F.R. Sections 1.97 and 1.98 will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. Section 371(c).

10. Additional documents:

a. International Publication No. WO01/02391
Specification, claims and drawings

b. Preliminary amendment (37 C.F.R. Section 1.121)

c. Notification of the Recording of a Change

11. The above items are being transmitted before 30 months from any claimed priority date.

AUTHORIZATION TO CHARGE ADDITIONAL FEES

The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No.: 19-4972

37 C.F.R. Section 1.492(a)(1), (2), (3), and (4) (filing fees)

37 C.F.R. Section 1.492(b), (c), and (d) (presentation of extra claims)

37 C.F.R. Section 1.17 (application processing fees)

37 C.F.R. Section 1.17(a)(1)-(5) (extension fees pursuant to Section 1.136(a))

37 C.F.R. Section 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. Section 1.311(b)).

Date: January 4, 2002

Harriet M. Strimpel, D. Phil.
Registration No. 37,008
Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110-1618
US
617-443-9292
Customer No. 02101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s):	Luscombe et al.	Attorney Docket: 2544/112	
Serial No.:	Not yet determined	Art Unit:	
Date Filed:	January 3, 2002	Examiner: Not yet determined	
For:	Therapeutic Agents	Date: January 4, 2002	

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Harriet M. Strimpel, D. Phil.

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Box PCT
Attention: EO/US
Commissioner for Patents
Washington, DC 20231

Preliminary Amendment

Dear Sir:

Please amend the International Application No. PCT/ EP00/05735 upon entry into the U.S. National Phase under Chapter II as follows:

In the claims:

Claims 1-23 are pending. Please amend claims 2-20. Please cancel claim 23.

2. Compounds according to claim 1, wherein A is-O-.

3. Compounds according to claim 1, wherein B is-O-.

4. Compounds according to claim 1, wherein g is 0, 1 or 2.

5. Compounds according to claim 1, wherein R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms,

hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached forming a fused benzene ring.

6. Compounds according to claim 1, wherein R_1 represents methoxy, fluoro, chloro, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached forming a fused benzene ring.

7. Compounds according to claim 1, wherein R_2 is H or an alkyl group containing 1 to 3 carbon atoms.

8. Compounds according to claim 1, wherein R_3 and R_4, which are the same or different, are H or methyl.

9. Compounds according to claim 1, wherein T is pyridyl, pyrimidinyl, pyrazinyl, phenyl, benzofuryl, 1,4-benzodioxanyl or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

10. Compounds according to claim 1, wherein T is 2-pyridyl, 2-pyrimidinyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo [b] furan-7 yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

11. Compounds according to claim 1, wherein R_5 is H or methyl.

12. Compounds according to claim 1, which are:

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrazin-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (3-chloropyrid-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (quinazolin-4-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine; N- (8-Methoxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-N'- [3- (trifluoromethyl)-2-pyridyl] ethanediamine;

N- (8-Methoxy-1, 2, 3, 4-tetrahydronaphth-2-ylmethyl)-1- [1-pyrimidin-2-yl) piperid-4- yl] methylamine;

7- {B-[1-(Pyrimidin-2-yl) piperid-4-ylmethyl] aminomethyl}-5,{B-[1-(Pyrimidin-2-yl) piperid-4-ylmethyl] aminomethyl}-5, 6, 7, 8-tetrahydronaphth-1ol;

N- (5-Methoxy-3, 4-dihydro-2H-1-benzopyran-3-ylmethyl)-1- [1-(pyrimidin-2-yl) piperid 4-yl] methylamine; N- (1, 4-Benzodioxan-2-ylmethyl)-1-(1-phenylpiperid-4-yl) methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (1, 4-benzodioxan-5-yl) piperid-4yl] methylamine;

1- [1- (1, 4-Benzodioxan-2-ylmethyl) piperid-4-yl]-N- (2-methoxyphenyl) methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (4-methoxyphenyl) piperid-4-yl] methylamine;

N- (8-Methoxy-1, 4-benzodioxan-2-ylmethyl)-N- (2-methoxyphenyl)-1, 3-propanediamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (3-methoxyphenyl) piperid-4-yl] methylamine;

N- (6, 7-Dichloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-chlorophenyl) piperid-4-yl] methylamine;

N- (5-Fluoro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-Fluoro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

1- [1- (2-methoxyphenyl) piperid-4-yl]-N- (naphtho [1, 2-b] dioxan-2ylmethyl) methylamine; 1- [1- (2, 3-Dihydrobenzo [b] furan-7-yl) piperid-4-yl]-N- (8-methoxy-1, 4-benzodioxan-2- ylmethyl) methylamine;

N- (6-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (7-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- (1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-hydroxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine; [and] or pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

13. Compounds according to claim 12, which are:

(S)- (-)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

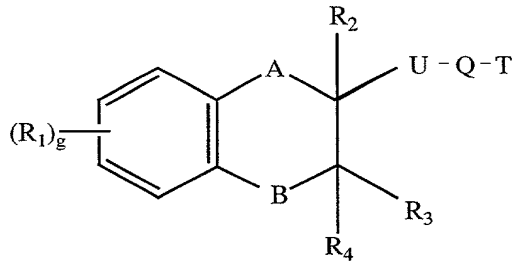
(R)- (+)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

(-)-N- (1, 4-Benzodioxan-2-ylmethyl)-l- [l- (pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride; or

(+)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride.

14. A method for reducing cravings to food or an addictive substance, comprising:

administering a therapeutically effective amount of a compound of formula I



or pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers, in which:

A is-0-;

Bis-0-;

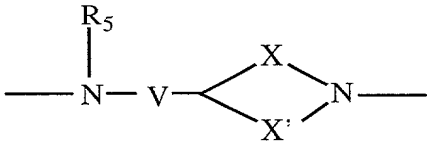
g is 0 or 1;

R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or hydroxy;

R_2, R_3 and R_4 are each H;

U is methylene;

Q is a group of formula Ila



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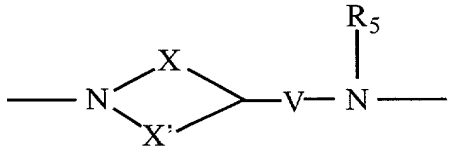


in which V is methylene or ethylene; X is an alkylene chain containing 0 to 2 carbon atoms and X'is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X' amounts to 3 or 4; and R_5 is H; and
T is pyridyl, pyrazinyl, phenyl, benzo [b] furanyl, 1,4-benzodioxanyl, or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

15. A method according to claim 14 wherein R_1 represents methoxy, fluoro, chloro or hydroxy.

16. A method according to claim 14, wherein T is 2pyridyl, 2-pyrazinyl, phenyl, 2, 3-dihydrobenzo [b] furan-7-yl, 1, 4-benzodioxan-5-yl or 4quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

17. A method according to claim 14, wherein the compounds of formula 1 are selected from:

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrazin-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (3-chloropyrid-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (quinazolin-4-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine;

N- (8-Methoxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- (1-phenylpiperid-4-yl) methylamine; N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (1, 4-benzodioxan-5-yl) piperid-4yl] methylamine;

1- [1- (1, 4-Benzodioxan-2-ylmethyl) piperid-4-yl]-N- (2-methoxyphenyl) methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (4-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (3-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-chlorophenyl) piperid-4-yl] methylamine;

N- (5-Fluoro-1, 4-benzodioxan-2-ylmethyl)-l- [l- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-Fluoro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

1- [1- (2, 3-Dihydrobenzo [b] furan-7-yl) piperid-4-yl]-N- (8-methoxy-1, 4-benzodioxan-2- ylmethyl) methylamine;

N- (6-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (7-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-hydroxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine; and

pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

18. A method according to claim 14 wherein the compounds of formula 1 are selected from:

(S)- (-)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4- yl] methylamine;

(R)- (+)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

(-)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride; and

(+)-N-(1, 4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride.

19. A method according to claim 14 wherein the compounds of formula 1 are selected from:

N- (7-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl]methylamine; and

pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

20. A method for reducing cravings to food or an addictive substance, comprising:

administering a therapeutically effective amount of a compound of formula 1, together with a pharmaceutically acceptable diluent or carrier in reducing cravings to food or an addictive substance.

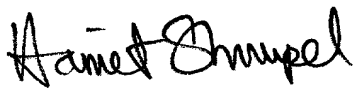
Remarks

Claims 2-20 have been amended and claim 23 has been canceled. Support for "administering a therapeutically effective amount" can be found on page 7, line 25 and pages 8-12 of the above application.

Conclusion

All claims presently in the application are believed to be allowable over the art of record and early notice to that effect is respectfully solicited. Please charge any additional fee required for the timely consideration of this application to Deposit Account No. 19-4972.

Respectfully submitted,



Harriet M. Strimpel, D.Phil.
Registration No. 37,008
Attorney for Applicant
Bromberg & Sunstein
125 Summer Street
Boston, MA 02110
617/443 9292

January 4, 2002
02544/00001 186076.1

Version with Markings to show Changes Made according to (37 CFR 1.121)

2. [The use of] C[c]ompounds [of formula I as claimed in] according to claim 1, wherein A is-O-.

3. [The use of] C[c]ompounds [of formula I as claimed in] according to [any preceding claim] according to claim 1, wherein B is-O-.

4. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein g is 0, 1 or 2.

5. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached forming a fused benzene ring.

6. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein R_1 represents methoxy, fluoro, chloro, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached forming a fused benzene ring.

7. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein R_2 is H or an alkyl group containing 1 to 3 carbon atoms.

8. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein R3 and R4, which are the same or different, are H or methyl.

9. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein T is pyridyl, pyrimidinyl, pyrazinyl, phenyl,

benzofuryl, 1,4-benzodioxanyl or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

10. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein T is 2-pyridyl, 2-pyrimidinyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo [b] furan-7 yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

11. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, wherein R5 is H or methyl.

12. [The use of] C[c]ompounds [of formula I as claimed in any preceding claim] according to claim 1, which are:

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrazin-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (3-chloropyrid-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (quinazolin-4-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine;

N- (8-Methoxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-N'- [3- (trifluoromethyl)-2-pyridyl] ethanediamine;

N- (8-Methoxy-1, 2, 3, 4-tetrahydronaphth-2-ylmethyl)-1- [1-pyrimidin-2-yl) piperid-4- yl] methylamine;

7- {B-[1-(Pyrimidin-2-yl) piperid-4-ylmethyl] aminomethyl}-5,{B-[1-(Pyrimidin-2-yl) piperid-4-ylmethyl] aminomethyl}-5, 6,7,8-tetrahydronaphth-1ol;

N- (5-Methoxy-3, 4-dihydro-2H-1-benzopyran-3-ylmethyl)-l- [l-(pyrimidin-2-yl) piperid 4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- (1-phenylpiperid-4-yl) methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (1, 4-benzodioxan-5-yl) piperid-4yl] methylamine;

1- [1- (1, 4-Benzodioxan-2-ylmethyl) piperid-4-yl]-N- (2-methoxyphenyl) methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (4-methoxyphenyl) piperid-4-yl] methylamine;

N- (8-Methoxy-1, 4-benzodioxan-2-ylmethyl)-N- (2-methoxyphenyl)-1,3-propanediamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-l- [l- (3-methoxyphenyl) piperid-4-yl] methylamine;

N- (6, 7-Dichloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-chlorophenyl) piperid-4-yl] methylamine;

N- (5-Fluoro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-Fluoro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

1-[1- (2-methoxyphenyl) piperid-4-yl]-N- (naphtho [1,2-b] dioxan-2ylmethyl) methylamine;

1- [1- (2, 3-Dihydrobenzo [b] furan-7-yl) piperid-4-yl]-N- (8-methoxy-1, 4-benzodioxan-2- ylmethyl) methylamine;

N- (6-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (7-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- (1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-hydroxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine; [and] or

pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

13. [The use of] C[c]ompounds [of formula I as claimed in] according to claim 12, which are:

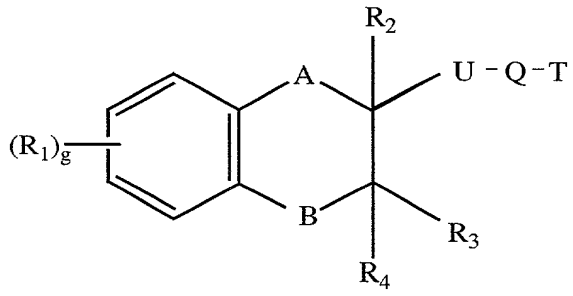
(S)- (-)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

(R)- (+)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

(-)-N- (1, 4-Benzodioxan-2-ylmethyl)-l- [l- (pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride; or

(+)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride.

14. [The use of] A method for reducing cravings to food or an addictive substance, comprising: administering a therapeutically effective amount of a compound[s] of formula I



[and] or pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers, in which:

A is-0-;

Bis-0-;

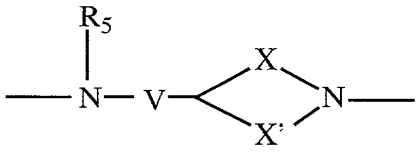
g is 0 or 1;

R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or hydroxy;

R_2, R_3 and R_4 are each H;

U is methylene;

Q is [a group of formula] Ila



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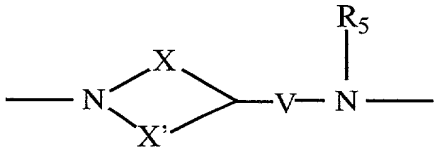


in which V is methylene or ethylene; X is an alkylene chain containing 0 to 2 carbon atoms and X'is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X' amounts to 3 or 4; and R_5 is H; and
T is pyridyl, pyrazinyl, phenyl, benzo [b] furanyl, 1,4-benzodioxanyl, or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo[; for use in reducing cravings to food or an addictive substance].

16. [The use of compounds of formula I as claimed in] A method according to claim 14, wherein T is 2pyridyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzoLb] furan-7-yl, 1,4-benzodioxan-5-yl or 4quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

17. [The use of compounds of formula I as claimed in] A method according to claim 14, wherein the compounds of formula 1 are selected from:

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrazin-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (3-chloropyrid-2-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (quinazolin-4-yl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine;

N- (8-Methoxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- (1-phenylpiperid-4-yl) methylamine;
N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (1, 4-benzodioxan-5-yl) piperid-4yl] methylamine;

1- [1- (1, 4-Benzodioxan-2-ylmethyl) piperid-4-yl]-N- (2-methoxyphenyl) methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (4-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (3-methoxyphenyl) piperid-4-yl] methylamine;

N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-chlorophenyl) piperid-4-yl] methylamine;

N- (5-Fluoro-1, 4-benzodioxan-2-ylmethyl)-l- [l- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-Fluoro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

1- [1- (2, 3-Dihydrobenzo [b] furan-7-yl) piperid-4-yl]-N- (8-methoxy-1,4-benzodioxan-2- ylmethyl) methylamine;

N- (6-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine ;

N- (7-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

N- (8-hydroxy-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine; and

pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

18. [The use of compounds of formula I as claimed in]A method according to claim 14 wherein the compounds of formula 1 are selected from: [which are:]

(S)- (-)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4- yl] methylamine;

(R)- (+)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl] methylamine;

(-)-N- (1, 4-Benzodioxan-2-ylmethyl)-1- [1- (pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride ; and

(+)-N-(1, 4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl) piperid-4-yl] methylamine dihydrochloride.

19. [The compound of formula I as claimed in] A method according to claim 14 wherein the compounds of formula 1 are selected from: [which is:]

N- (7-Chloro-1, 4-benzodioxan-2-ylmethyl)-1- [1- (2-methoxyphenyl) piperid-4yl]methylamine; and

pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

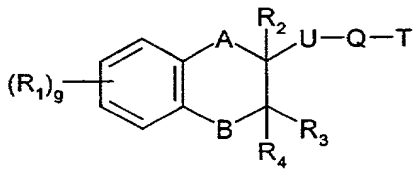
20. A method for reducing cravings to food or an addictive substance, [The use of pharmaceutical compositions] comprising: administering a therapeutically effective amount of a compound of formula 1, together with a pharmaceutically acceptable diluent or carrier in reducing cravings to food or an addictive substance.

Therapeutic Agents

The present invention relates to the use of compounds for reducing cravings for food or an addictive substance in mammals particularly human beings.

WO95/07274 discloses the use of a compounds of formula I as shown below as novel compounds useful for treating depression, anxiety, psychoses, tardive dyskinesia, Parkinson's disease, obesity, hypertension, Tourette's syndrome, sexual dysfunction, drug addiction, drug abuse, cognitive disorders, Alzheimer's disease, senile dementia, obsessive-compulsive behaviour, panic attacks, eating disorders, anorexia, cardiovascular and cerebrovascular disorders, non-insulin dependent diabetes mellitus, hyperglycaemia, constipation, arrhythmia, disorders of the neuroendocrine system, stress, prostatic hypertrophy, or spasticity.

The present invention provides compounds of formula I



including pharmaceutically acceptable salts thereof in which

A is methylene or -O-;

B is methylene or -O-;

g is 0, 1, 2, 3 or 4;

R_1 represents a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl

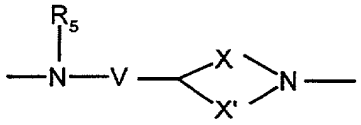
group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring, the substituents represented by R_1 being the same or different when g is 2, 3 or 4;

R_2 is H, an alkyl group containing 1 to 3 carbon atoms, or an alkoxy group containing 1 to 3 carbon atoms;

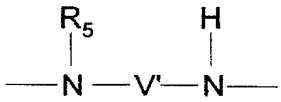
R_3 and R_4, which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

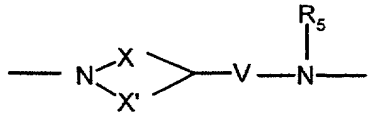
Q represents a divalent group of formula IIa, IIb or IIc



IIa



IIb



IIc

in which V is a bond or an alkylene chain containing 1 to 3 carbon atoms optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

V′ is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

X is an alkylene chain containing 0 to 2 carbon atoms and X′ is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X′ amounts to 3 or 4; R_5 is H or an alkyl group containing 1 to 3 carbon atoms; and

T represents an aromatic group optionally containing one or more N atoms and optionally substituted by one or more substituents selected from halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or a polyhalogenated alkyl group, for example trifluoromethyl, or T represents benzo[b]furanyl or benzodioxanyl with the proviso that T is not 2-pyrimidinyl when A is -O- for use in reducing cravings to food or an addictive substance.

In preferred compounds of formula I, A is -O-.

In preferred compounds of formula I, B is -O-.

In more preferred compounds of formula I both A and B are -O-.

In preferred compounds of formula I, g is 0, 1 or 2.

In preferred compounds of formula I, R_1 represents halo (for example fluoro, chloro, or bromo), an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring. In more preferred compounds of formula I, R_1 represents methoxy, fluoro, chloro, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring.

In preferred compounds of formula I, R_2 is H or an alkyl group containing 1 to 3 carbon atoms. In more preferred compounds of formula I, R_2 is H.

In preferred compounds of formula I, R_3 and R_4, which are the same or different, are H or methyl. In more preferred compounds of formulaI, R_3 and R_4 are both H.

In preferred compounds of formula I, U is methylene.

In preferred compounds of formula I in which Q is a group of formula IIa or IIc, V is methylene or ethylene.

In preferred compounds of formula I, in which Q is a group of formula IIb, V′ is an alkylene chain containing 2 to 4 carbon atoms.

In preferred compounds of formula I, R_5 is H or methyl. In more preferred compounds of formula I, R_5 is H.

In preferred compounds of formula I, T is pyridyl, pyrimidinyl, pyrazinyl, phenyl, benzo[b]furanyl, 1,4-benzodioxanyl or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo (eg fluoro, chloro or bromo). In more preferred compounds of formula I, T is 2-pyridyl, 2-pyrimidinyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo[b]furan-7-yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo (eg fluoro, chloro or bromo).

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and their salts may exist in the form of solvates (for example hydrates).

Compounds of formula I contain one or more chiral centres, and exist in different optically active forms. When compounds of formula I contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be

resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of formula I contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to this skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of formula I and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof. Certain compounds of formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Specific compounds of formula I are:-

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrazin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-chloropyrid-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(quinazolin-4-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-N'-[3-(trifluoromethyl)-2-pyridyl]ethanediamine;

N-(8-Methoxy-1,2,3,4-tetrahydronaphth-2-ylmethyl)-1-[1-pyrimidin-2-yl)piperid-4-yl]methylamine;

7-{N-[1-(Pyrimidin-2-yl)piperid-4-ylmethyl]aminomethyl}-5,6,7,8-tetrahydronaphth-1-ol;

N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-ylmethyl)-1-[1-(pyrimidin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-(1-phenylpiperid-4-yl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(1,4-benzodioxan-5-yl)piperid-4-yl]methylamine;

1-[1-(1,4-Benzodioxan-2-ylmethyl)piperid-4-yl]-N-(2-methoxyphenyl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(4-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-N'-(2-methoxyphenyl)-1,3-propanediamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-methoxyphenyl)piperid-4-yl]methylamine;

N-(6,7-Dichloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-chlorophenyl)piperid-4-yl]methylamine;

N-(5-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

1-[1-(2-methoxyphenyl)piperid-4-yl]-N-(naphtho[1,2-b]dioxan-2-ylmethyl)methylamine;

1-[1-(2,3-Dihydrobenzo[b]furan-7-yl)piperid-4-yl]-N-(8-methoxy-1,4-benzodioxan-2-ylmethyl)methylamine;

N-(6-chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(7-chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-hydroxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

Specific enantiomeric forms of compounds of formula I include:

(S)-(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(R)-(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride;

(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride.

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or a salt thereof together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term "active compound" denotes a compound of formula I or a salt thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethyl- cellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, for example paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or ester or (b) solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose of part of a unit dose of active compound.

b) Tablets

Tablets are prepared from the following ingredients.

	Parts by weight
Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinyl-pyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate

and the rest of the starch. The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

Enteric coated tablets

Tablets are prepared by the method described in (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or III may be used to treat drug misuse or other addictive disorders. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history, and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

In another aspect the present invention provides a method of treating drug misuse or other addictive disorders which comprises the administration of a therapeutically effective amount of a compound of formula I to a patient in need thereof.

The present invention provides a method of reducing cravings to food or an addictive substance in a mammal comprising administering an effective amount of a compound of formula I to a mammal in need thereof.

Suitably the addictive substance is cocaine, amphetamine, nicotine, opiates, tobacco or alcohol. The addictive substance may also be MDMA (ecstasy), a cannabinoid, LSD, MDA or PCP. .The term opiates includes heroin and morphine.

In yet another aspect, the present invention provides the use of a compound of formula I or III in the manufacture of a medicament for use in the treatment ofdrug misuse or other addictive disorders.

Conditions which may be advantageously treated with the compounds of the present invention include disorders arising from drug misuse including drug withdrawal symptoms, aiding in the cessation of smoking, aiding in the prevention of relapse after cessation of drug use and similar use in the treatment of other addictive disorders such as compulsive gambling, compulsive shopping disorder and compulsive sexual disorder.

In another aspect the present invention provides a method of treating addictive-drug-induced psychoses comprising administering a therapeutically effective amount of a compound of formula I to a mammal, particularly a human being, in need thereof.

Addictive drugs which may cause psychoses include benzodiazepines, cannabinoids, LSD, MDMA, MDA, PCP, opiates including heroin and morphine, amphetamine, cocaine and alcohol.

The pharmacological activity of the compounds of the present invention may be demonstrated by one or more of the following tests.

STUDY 1 METHODS

Subjects: The subjects are four male rhesus monkeys *(Macaca mulatta),* weighing 5.7-8.1 kg and maintained on a diet of 3-4 monkey biscuits and one piece of fresh fruit per day. During the week, all food is delivered after the experimental session, whereas at weekends, food is delivered between 9 a.m. and noon. Water is

freely available at all times. The monkeys are housed in a humidity and temperature controlled room with a 12 h light-dark cycle (lights on from 7 a.m. to 7 p.m.).

Apparatus: Each monkey is housed individually in a well-ventilated, stainless steel chamber (56 x 71 x 69 cm) which includes an operant panel (28 x 28 cm) mounted on the front wall. Three response keys are arranged in a horizontal row 3.2 cm from the top of the operant panel. Each key can be transilluminated by red or green stimulus lights (Superbright LEDs). An externally mounted pellet dispenser delivers 1 g fruit-flavoured food pellets to a food receptacle beneath the operant response panel. A computer, located in a separate room, controls the operant panels and data collection.

Discrimination Training: Discrimination training is conducted 5 days per week during daily sessions composed of multiple cycles. Each cycle consists of a 15 min time-out period followed by a 5 min response period. During the time-out, all stimulus lights are off, and responding has no scheduled consequences. During the response period, the right and left response keys are transilluminated red or green, and monkeys can earn up to 10 food pellets by responding under a FR 30 schedule of food presentation. For one monkey, the left key is illuminated green and the right key is illuminated red, the colours of the response-keys are reversed for the other three monkeys. The centre key is not illuminated at any time and responding on it has no scheduled consequences. If all available food pellets are delivered before the end of the 5 min response period, the stimulus lights are turned off and responding has no scheduled consequences for the remainder of the 5 min period.

On training days, monkeys are given either saline or 0.40 mg/kg cocaine, i.m., 10 min before the response period. Following the administration of saline, responding on only the green key (the saline-appropriate key) produces food, whereas following administration of 0.40 mg/kg cocaine, only responding on the red key (the drug-appropriate key) produces food. Responses on the inappropriate key reset the FR requirement on the appropriate key. Sessions consist of 1 to 5 cycles and, if cocaine is administered, this occurs only during the last cycle. Thus, training days consist of 0 to 5 saline cycles followed by 0 or 1 cocaine cycle.

During each response period, 3 dependent variables are determined:

1) Percent injection-appropriate responding prior to delivery of the first reinforcer.

2) Percent injection-appropriate responding for the entire response period

3) Response Rate.

Monkeys meeting the following criteria during the training day immediately proceeding the test day and in at least 6 of 7 consecutive training sessions before this are used for discrimination testing:

1) the percent injection-appropriate responding prior to delivery of the first reinforcer is ≥ 80% for all cycles;

2) the percent injection-appropriate responding for the entire cycle is ≥ 90% for all cycles;

3) Response rates during saline training cycles are >0.5 responses per second.

If responding did not meet criterion levels of discrimination performance, then training is continued until criterion levels of performance are obtained for at least two consecutive days.

Discrimination Testing: Test sessions are identical to training sessions except that responding on either key produces food, and the test compound is administered using a Pretreatment Protocol. In this protocol, a cumulative dose-effect curve for cocaine (0.013-1.3 mg/kg) is determined either alone or following pretreatment with the test compound, which is administered 20 min before the first dose of cocaine.

Mean data from saline and drug cycles during the training day immediately proceeding the initial test day serve as the control data for the subsequent test day.

Data Analysis: The Percent Cocaine-Appropriate Responding and the Response Rate are plotted as a function of the dose of cocaine (log scale). Where possible, the ED_{50} value for cocaine is determined by drawing a line between the points above and below 50% cocaine-appropriate responding, and then using linear regression to interpolate the dose that would produce 50% cocaine-appropriate responding. ED_{50} values for cocaine administered alone and following pretreatment with the test compound are then compared.

Drugs: Cocaine hydrochloride is dissolved in sterile saline. The test compound is dissolved in 1% lactic acid in distilled water.

RESULTS

Control mean saline-appropriate responding = 99.8% (± 0.2) and 100% appropriate responding are obtained during cocaine cycles.

ED_{50} values for cocaine are calculated. Administration of cocaine alone produces a dose-dependent increase in cocaine-appropriate responding in all four monkeys. Complete substitution is obtained at the training dose of cocaine (0.4 mg/kg) in all monkeys, and a higher dose of 1.3 mg/kg usually decreases response rates. Pretreatment with 0.01 mg/kg of the test compound produces a rightward shift in the cocaine dose-effect curve and a 3-fold increase in the cocaine ED_{50} value in monkey 2, but it has no effect on the cocaine discrimination dose-effect curve in the other three monkeys. A higher dose of 0.032 mg/kg of the test compound produces rightward shifts in the cocaine dose-effect curves in all four monkeys. The test compound (0.01 and 0.032 mg/kg) also eliminated responding during the first one to three cycles of the cumulative cocaine dose-effect curve determination (i.e. in combination with 0.013 and 0.04 mg/kg cocaine). However, monkeys responded after administration of higher cocaine doses, thereby permitting evaluation of the effects on cocaine discrimination. Interestingly, response rates following administration of the highest dose of cocaine (1.3 mg/kg) are often higher following

test compound pretreatment than for cocaine alone, suggesting that the test compound attenuated the rate-decreasing effects of high cocaine doses.

These studies can establish that the test compound antagonises the discriminative stimulus effects and possibly also the rate decreasing effects of cocaine at doses that also produce effects on response rates by comparing ED_{50} values (mg/kg) for cocaine administered either alone or after pretreatment with test compound.

STUDY 2 METHODS

Subjects: The subjects are four male rhesus monkeys *(Macaca mulatta)*. Each monkey is maintained on a diet of 3 monkey biscuits and one piece of fresh fruit per day in addition to fruit-flavoured pellets delivered during operant sessions (see below). Water is freely available at all times. The monkeys are housed in a humidity and temperature controlled room with a 12 hr light-dark cycle (lights on from 7 a.m. to 7 p.m.).

Monkeys are surgically implanted with double-lumen silicone rubber catheters (inside diameter 0.7 mm, outside diameter 2.0 mm) to facilitate concurrent delivery of cocaine and treatment compounds. Catheters are implanted in the jugular or femoral vein and exteriorized in the midscapular region. All surgical procedures are performed under aseptic conditions. Monkeys are sedated with ketamine (5 mg/kg, s.c.), and anaesthesia is induced with sodium thiopental (10 mg/kg, i.v). Monkeys receive 0.05 mg/kg atropine, to reduce salivation. Following insertion of a tracheal tube, anaesthesia is maintained with isoflurane (1-1.5% in oxygen). After surgery, monkeys are administered aspirin or acetaminophen (80-160 mg/day; p.o.) for 3 days and Procaine Penicillin 0 (300,000 units/day, i.m.) every day for 5 days. The i.v. catheter is protected by a tether system consisting of a custom-fitted nylon vest connected to a flexible stainless steel cable and fluid swivel (Lomir Biomedical; Malone, NY), which permits the monkeys to move freely. Catheter patency is periodically evaluated by i.v. administration of the short-acting barbiturate methohexital (3 mg/kg i.v.) or ketamine (2-3 mg/kg i.v.). The catheter is considered

patent if i.v. administration of methohexital or ketamine produces loss of muscle tone within 10 seconds after its administration.

Apparatus: Each monkey is housed individually in a well-ventilated stainless steel chamber (64 x 64 x 79 cm which includes an operant panel (28 x 28 cm) mounted on the front wall. Three response keys (6.4 x 6.4 cm) are arranged in a horizontal row 3.2 cm from the top of the operant panel. Each key can be transilluminated by red or green stimulus lights (Superbright LEDs). An externally mounted pellet dispenser delivers 1 g fruit-flavoured food pellets to a food receptacle beneath the operant response panel. Two syringe pumps are mounted above each cage for delivery of saline or drug solutions through the intravenous catheters. Operant panels and data collection are controlled by a computer through a MED-PC interface.

Training: As shown in the diagram below, food and i.v. drug or saline injections are available during three alternating components: a 5 min food component, a 100-min drug component, and a second 5 min food component. Both food and i.v. injections are available under a FR 30 schedule of reinforcement. During the two food components, the response key is transilluminated red. During the drug component, the response key is transilluminated green. Following the delivery of each food pellet or drug injection, there is a 10 sec timeout period, during which the stimulus light illuminating the centre response key is turned off and responding has no scheduled consequences. The food and drug components are separated by 5-min timeout periods when the response key is dark, and responding has no scheduled consequences. The entire food/drug/food session lasts 120 min.

In addition to the food/drug/food session described above, monkeys are also given the opportunity to self-administer additional food pellets during supplementary food sessions. During these sessions, food is available under a FR30/Timeout 10 sec schedule, and a maximum of 25 pellets per session can be earned. These food sessions provide additional enrichment opportunities for the monkeys and behavioural information relevant for the evaluation of prolonged treatment drug effects.

During training, the solution available for self-administration during the drug component is alternated between 0.032 mg/kg/inj cocaine (the maintenance dose of cocaine) and saline. Each period of cocaine or saline availability usually lasts from 3 to 10 days. Monkeys are trained until they met the following criteria for stable cocaine self-administration: 1) three consecutive days during which the response rate during the drug component of each session differs by no more than 20% from the mean drug component response rate and there is no upward or downward trend; and 2) rapid saline extinction as indicated by a decrease in drug component response rates on the first day of saline substitution.

Evaluation of Test Compound: The effects of the test compound (0.0032-0.10 mg/kg) on cocaine self-administration and food-maintained behaviour are evaluated using the standard pretreatment test procedure. In this procedure, the test compound is administered i.m. 20-min prior to a test session during which a test unit dose of cocaine is available during the drug component. Two series of studies are described here. In the first, the unit dose of cocaine is 0.0032 mg/kg/inj (at or near the peak of each monkey's cocaine self-administration dose-effect curve) and the effects of pretreatment with each dose of test compound are determined in single sessions for all monkeys. In the second series of studies, the effects of pretreatment with each of two doses of the test compound (0.003 and 0.01 mg/kg) on the entire cocaine dose-effect function are determined. In these studies, the dose of cocaine is systematically varied for single test sessions after pretreatment with each dose of the test compound. Both the dose of cocaine and the pretreatment dose of the test compound are varied across test sessions in an irregular order among monkeys.

At the conclusion of each pretreatment test in either series of studies, training conditions (availability of saline or the maintenance dose of cocaine) are reinstated. Test sessions generally are conducted on Tuesdays and Fridays, and either saline or the maintenance dose of cocaine is available during training sessions for the remainder of the week. On occasion, another dose of cocaine is substituted for the maintenance dose to insure that the position of the cocaine dose-effect function in individual monkeys is stable. In addition, test days are occasionally omitted to allow several days of saline substitution.

Data Analysis: The dependent variables are the response rates during each food and drug component. The response rate is calculated as [total # responses (component duration - S timeouts)]. Control response rates for each food and drug component during availability of each unit dose of cocaine are defined as the response rate obtained when that unit dose of cocaine is available and no pretreatment is administered. The ED_{50} value for the test compound during each food or drug component is defined as the dose of the test compound that decreases rates of cocaine or food self-administration to 50% of control response rates. The ED_{50} values are determined where possible by linear regression from the linear portion of the test compound dose-effect curve.

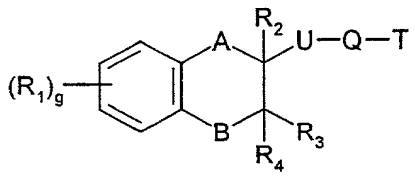
For subsequent studies, in which the unit dose of cocaine is varied and the pretreatment dose of the test compound is held constant, response rates are graphed as a function of the unit dose of cocaine. Control cocaine dose-effect curves are determined in the absence of pretreatment and are visually compared to cocaine dose-effect curves determined following pretreatment with the test compound.

Drugs: Cocaine hydrochloride is dissolved in saline. A stock solution of 10 mg/ml of the test compound is prepared using a vehicle of 1% lactic acid in distilled water, and dilutions are made with distilled water. Aseptic precautions are taken in every phase of cocaine solution preparation and dispensing. Cocaine solutions are filter-sterilised using a 0.22 micron Millipore Filter and stored in sterile, pyrogen-free vials. Sterility of the entire fluid path for drug solutions is maintained throughout the study. Each unit dose of cocaine is delivered i.v. in an injection volume of 0.1 ml. Doses of the test compound are delivered i.m. in a volume of 0.2-3.0 ml.

These studies can establish that treatment with the test compound diminishes cocaine self-administration and food-maintained behaviour.

Claims

1. Compounds of formula I



including pharmaceutically acceptable salts thereof in which

A is methylene or -O-;

B is methylene or -O-;

g is 0, 1, 2, 3 or 4;

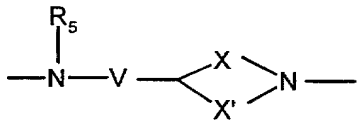
R_1 represents a) halo, b) an alkyl group containing 1 to 3 carbon atoms optionally substituted by one or more halo, c) an alkoxy group containing 1 to 3 carbon atoms optionally substituted by one or more halo, d) an alkylthio group containing 1 to 3 carbon atoms optionally substituted by one or more halo, e) hydroxy, f) an acyloxy group containing 1 to 3 carbon atoms, g) hydroxymethyl, h) cyano, i) an alkanoyl group containing 1 to 6 carbon atoms, j) an alkoxycarbonyl group containing 2 to 6 carbon atoms, k) a carbamoyl group or carbamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, l) a sulphamoyl or sulphamoylmethyl group each optionally N-substituted by one or two alkyl groups each containing 1 to 3 carbon atoms, m) an amino group optionally substituted by one or two alkyl groups each containing 1 to 3 carbon atoms; or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring, the substituents represented by R_1 being the same or different when g is 2, 3 or 4;

R_2 is H, an alkyl group containing 1 to 3 carbon atoms, or an alkoxy group containing 1 to 3 carbon atoms;

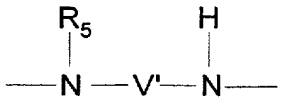
R_3 and R_4, which are the same or different, are H, or an alkyl group containing 1 to 3 carbon atoms;

U is an alkylene chain containing 1 to 3 carbon atoms, optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

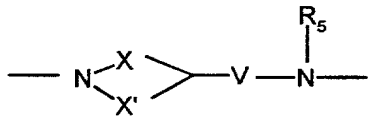
Q represents a divalent group of formula IIa, IIb or IIc



IIa



IIb



IIc

in which V is a bond or an alkylene chain containing 1 to 3 carbon atoms optionally substituted by one or more alkyl groups each containing 1 to 3 carbon atoms;

V′ is an alkylene chain containing 2 to 6 carbon atoms, optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

X is an alkylene chain containing 0 to 2 carbon atoms and X′ is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X′ amounts to 3 or 4;

R_5 is H or an alkyl group containing 1 to 3 carbon atoms; and

T represents an aromatic group optionally containing one or more N atoms and optionally substituted by one or more substituents selected from halo, an alkyl

group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or a polyhalogenated alkyl group, or T represents benzo[b]furanyl or benzodioxanyl with the proviso that T is not 2-pyrimidinyl when A is –O-; for use in reducing cravings to food or an addictive substance.

2. The use of compounds of formula I as claimed in claim 1 wherein A is -O-.

3. The use of compounds of formula I as claimed in any preceding claim wherein B is -O-.

4. The use of compounds of formula I as claimed in any preceding claim wherein g is 0, 1 or 2.

5. The use of compounds of formula I as claimed in any preceding claim wherein R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring.

6. The use of compounds of formula I as claimed in any preceding claim wherein R_1 represents methoxy, fluoro, chloro, hydroxy, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring.

7. The use of compounds of formula I as claimed in any preceding claim wherein R_2 is H or an alkyl group containing 1 to 3 carbon atoms.

8. The use of compounds of formula I as claimed in any preceding claim wherein R_3 and R_4, which are the same or different, are H or methyl.

9. The use of compounds of formula I as claimed in any preceding claim wherein T is pyridyl, pyrimidinyl, pyrazinyl, phenyl, benzofuryl, 1,4-benzodioxanyl or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

10. The use of compounds of formula I as claimed in any preceding claim wherein T is 2-pyridyl, 2-pyrimidinyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo[b]furan-7-

yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

11. The use of compounds of formula I as claimed in any preceding claim wherein R_5 is H or methyl.

12. The use of compounds of formula I as claimed in claim 1 which are:

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrazin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-chloropyrid-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(quinazolin-4-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-N'-[3-(trifluoromethyl)-2-pyridyl]ethanediamine;

N-(8-Methoxy-1,2,3,4-tetrahydronaphth-2-ylmethyl)-1-[1-pyrimidin-2-yl)piperid-4-yl]methylamine;

7-{N-[1-(Pyrimidin-2-yl)piperid-4-ylmethyl]aminomethyl}-5,6,7,8-tetrahydronaphth-1-ol;

N-(5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-ylmethyl)-1-[1-(pyrimidin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-(1-phenylpiperid-4-yl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(1,4-benzodioxan-5-yl)piperid-4-yl]methylamine;

1-[1-(1,4-Benzodioxan-2-ylmethyl)piperid-4-yl]-N-(2-methoxyphenyl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(4-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-N'-(2-methoxyphenyl)-1,3-propanediamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-methoxyphenyl)piperid-4-yl]methylamine;

N-(6,7-Dichloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-chlorophenyl)piperid-4-yl]methylamine;

N-(5-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

1-[1-(2-methoxyphenyl)piperid-4-yl]-N-(naphtho[1,2-b]dioxan-2-ylmethyl)methylamine;

1-[1-(2,3-Dihydrobenzo[b]furan-7-yl)piperid-4-yl]-N-(8-methoxy-1,4-benzodioxan-2-ylmethyl)methylamine;

N-(6-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(7-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-hydroxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

13. The use of compounds of formula I as claimed in claim 12 which are:-

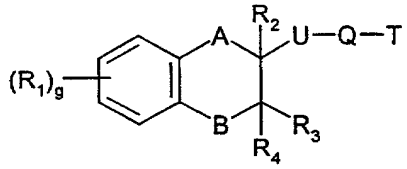
(S)-(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(R)-(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride;

(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride.

14) The use of compounds of formula I



and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers, in which

A is -O-;

B is -O-;

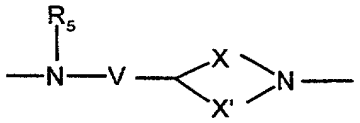
g is 0 or 1;

R_1 represents halo, an alkyl group containing 1 to 3 carbon atoms, an alkoxy group containing 1 to 3 carbon atoms, or hydroxy;

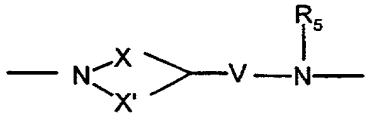
R_2, R_3 and R_4 are each H;

U is methylene;

Q is a group of formula IIa or IIc



IIa



IIc

in which V is methylene or ethylene; X is an alkylene chain containing 0 to 2 carbon atoms and X′ is an alkylene chain containing 1 to 4 carbon atoms provided that the total number of carbon atoms in X and X′ amounts to 3 or 4; and R_5 is H; and

T is pyridyl, pyrazinyl, phenyl, benzo[b]furanyl, 1,4-benzodioxanyl, or quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo; for use in reducing cravings to food or an addictive substance.

15) The use of compounds of formula I as claimed in claim 14 wherein R_1 represents methoxy, fluoro, chloro or hydroxy.

16) The use of compounds of formula I as claimed in claim 14 wherein T is 2-pyridyl, 2-pyrazinyl, phenyl, 2,3-dihydrobenzo[b]furan-7-yl, 1,4-benzodioxan-5-yl or 4-quinazolinyl all optionally substituted by methoxy, trifluoromethyl, or halo.

17) The use of compounds of formula I as claimed in claim 14 selected from:

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrazin-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-chloropyrid-2-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(quinazolin-4-yl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine;

N-(8-Methoxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-(1-phenylpiperid-4-yl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(1,4-benzodioxan-5-yl)piperid-4-yl]methylamine;

1-[1-(1,4-Benzodioxan-2-ylmethyl)piperid-4-yl]-N-(2-methoxyphenyl)methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(4-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(3-methoxyphenyl)piperid-4-yl]methylamine;

N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-chlorophenyl)piperid-4-yl]methylamine;

N-(5-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-Fluoro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

1-[1-(2,3-Dihydrobenzo[b]furan-7-yl)piperid-4-yl]-N-(8-methoxy-1,4-benzodioxan-2-ylmethyl)methylamine;

N-(6-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(7-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

N-(8-hydroxy-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

18) The use of compounds of formula I as claimed in claim 14 which are:-

(S)-(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(R)-(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

(-)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride;

(+)-N-(1,4-Benzodioxan-2-ylmethyl)-1-[1-(pyrid-2-yl)piperid-4-yl]methylamine dihydrochloride.

19) The compound of formula I as claimed in claim 14 which is:

N-(7-Chloro-1,4-benzodioxan-2-ylmethyl)-1-[1-(2-methoxyphenyl)piperid-4-yl]methylamine;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

20. The use of pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I, together with a pharmaceutically acceptable diluent or carrier in reducing cravings to food or an addictive substance.

21. A method of reducing cravings to food or an addictive substance which comprises the administration of a therapeutically effective amount of a compound of formula I as claimed in any of claims 1 to 19 to a patient in need thereof.

22. A method as claimed in claim 15 wherein the addictive substance is cocaine, amphetamine, nicotine, opiates, tobacco, alcohol or ecstasy.

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(71) Applicant *(for all designated States except US)*: **KNOLL AKTIENGESELLSCHAFT** [DE/DE]; D-67061 Ludwigshafen (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LUSCOMBE, Graham, Paul** [GB/GB]; R3 Pennyfoot Street, Nottingham NG1 1GF (GB). **NEEDHAM, Patricia, Lesley** [GB/GB]; R3 Pennyfoot Street, Nottingham NG1 1GF (GB).

(74) Agent: **GOLDSCHEID, Bettina**; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
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(88) Date of publication of the international search report:
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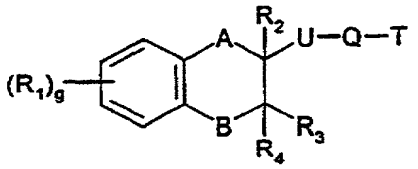
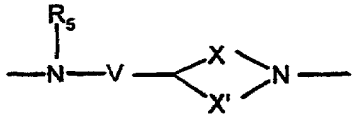
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BICYCLIC AROMATIC COMPOUNDS FOR TREATING DRUG ADDICTION



(I)



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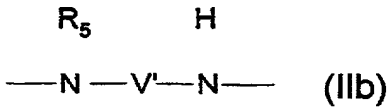

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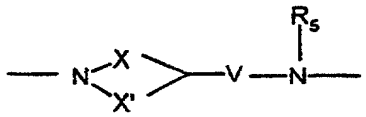

(IIc)

(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof in which A is methylene or -O-; B is methylene or -O-; and g is 0, 1, 2, 3 or 4; R_1 represents, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkylthio, hydroxy, acyloxy, hydroxymethyl, cyano, alkanoyl, alkoxycarbonyl, optionally N-substituted carbamoyl, carbamoylmethyl, sulphamoyl or sulphamoylmethyl, an amino group optionally substituted by one or two alkyl groups, or two adjacent R_1 groups together with the carbon atoms to which they are attached form a fused benz ring; R_2 is H, alkyl or alkoxy; R_3 and R_4, which are the same or different, are H, or alkyl; U is an alkylene chain optionally substituted by one or more alkyl; Q represents a divalent group of formula (IIa, IIb or IIc) in which V is a bond or an alkylene chain optionally substituted by one or more alkyl; V' is an alkylene chain optionally substituted by one or more alkyl; X is a bond or an alkylene chain and X' is an alkylene chain, provided that the total number of carbon atoms in X and X' amounts to 3 or 4; R_5 is H, or alkyl; and T represents an optionally substituted aromatic group which optionally contains one or more N atoms, provided that T is not 2-pyrimidinyl when A is -O-; have utility in reducing cravings to food or an addictive substance.

WO 01/02391 A3

SEND CORRESPONDENCE TO

Harriet M. Strimpel
Bromberg & Sunstein LLP
125 Summer Street
Boston, MA 02110-1618
US

Customer Number 02101

DIRECT TELEPHONE CALLS TO:

Harriet M. Strimpel
617-443-9292

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Graham Paul Luscombe
Inventor's signature _____
Date _____ **Country of Citizenship** Great Britain
Residence Nottingham, Great Britain
Post Office Address R3 Pennyfoot Street, Nottingham NG1 1GF, Great Britain

2000

Patricia Lesley Needham
Inventor's signature x Patricia Lesley Needham
Date 13 March, 2002 **Country of Citizenship** Great Britain
Residence Nottingham, Great Britain GB3
Post Office Address R3 Pennyfoot Street, Nottingham NG1 1GF, Great Britain

23. The use of a compound of formula I as claimed in any of claims 1 to 19 in the manufacture of a medicament for use in reducing cravings to food or an addictive substance.

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SIGNATURE(S)

Graham Paul Luscombe
Inventor's signature Graham Paul Luscombe
Date March 18th 2002 **Country of Citizenship** Great Britain
Residence Nottingham, Great Britain GB3
Post Office Address R3 Pennyfoot Street, Nottingham NG1 1GF, Great Britain

Patricia Lesley Needham
Inventor's signature _____
Date _____ **Country of Citizenship** Great Britain
Residence Nottingham, Great Britain
Post Office Address R3 Pennyfoot Street, Nottingham NG1 1GF, Great Britain

POWER OF ATTORNEY

I hereby appoint the following practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

APPOINTED PRACTITIONER(S)	REGISTRATION NUMBER(S)
Harriet M. Strimpel	37,008
Bruce D. Sunstein	27,234
Robert M. Asher	30,445
Timothy M. Murphy	33,198
Steven G. Saunders	36,265
Karen A. Buchanan	37,790
Samuel J. Petuchowski	37,910
Jeffrey T. Klayman	39,250
John J. Stickevers	39,387
Elizabeth P. Morano	42,904
Jean M. Tibbetts	43,193
Jay Sandvos	43,900
Keith J. Wood	45,235
Alton Hornsby, III	47,299
Alexander J. Smolenski	47,953
John L. Conway	48,241

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PRIOR PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS APPLICATION AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. SECTION 119(a)-(d)

INDICATE IF PCT	APPLICATION NUMBER	DATE OF FILING DAY, MONTH, YEAR	PRIORITY CLAIMED UNDER 35 U.S.C. SECTION 119
PCT	EP00/05735	21 June 2000	Yes
GB	9915616.8	05 July 1999	Yes

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PCT	EP00/05735	21 June 2000	Yes
GB	9915616.8	05 July 1999	Yes

78617/005

Practitioner's Docket No. 2544/112 *PATENT*

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is for a national stage of PCT application.

INVENTORSHIP IDENTIFICATION

My residence, post office address and citizenship are as stated below, next to my name. I believe that I am an original, first and joint inventor of the subject matter that is claimed, and for which a patent is sought on the invention entitled:

TITLE OF INVENTION

Therapeutic Agents

SPECIFICATION IDENTIFICATION

The specification was described and claimed in PCT International Application No. PCT/EP00/05735, filed on 21 June, 2000.

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in 37, Code of Federal Regulations, Section 1.56.

PRIORITY CLAIM (35 U.S.C. Section 119(a)-(d))

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

Such applications have been filed as follows.

78617005

Practitioner's Docket No. 2544/112 ***PATENT***

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION, OR C-I-P)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

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